

Appl. No. 10/751,545
Reply to Office Action of March 26, 2007

Docket No. DEAV2003/0002 US NP

REMARKS

Reconsideration of the Examiner's rejection of the present application is requested respectfully in view of the following remarks.

STATUS OF THE CLAIMS

At the time of the present Office Action, claims 1-9. No claims are amended, added or deleted. Therefore, claims 1-9 are presented for consideration.

SUMMARY OF OFFICE ACTION

Claims 1-9 also stand rejected under 35 U.S.C. §103(a) as being unpatentable over Barvian et al, WO 02/064571 (hereinafter Barvian).

Claims 1-9 stand rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-17 of Weithmann et al, U.S. Patent No. 6,933,298 (hereinafter Weithmann).

Claims 1-9 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-12 of copending Klingler et al, Application No. 10/700,273 (hereafter Klingler '273).

DISCUSSION

The present paper is presented in response to the Final Office Action in which the Examiner raised objections to some of the arguments presented in the prior response of December 13, 2006. The arguments presented in the prior response are again presented, as background to the present discussion.

The present invention is directed to a specific class of pyrimidine-4,6-dicarboxylic acid diamide (hereinafter PDDA) compounds as defined in claim 1 which have been discovered to have a unique combination of properties particularly useful for selectively inhibiting collagenase matrix metalloproteinase (MMP) 13 in the treatment of a degenerative joint disease such as osteoarthritis. MMPs are a broad class of enzymes which exhibit many

Appl. No. 10/751,545

Docket No. DEAV2003/0002 US NP

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types of bioactivity. For example, MMPs are known which act to cleave collagen, laminin, proteoglycans, elastin or gelatin, and thus play an important role in bone and connective tissue. Some of these functions are useful in treating certain diseases, while other functions may be detrimental. As discussed, among other places, at page 19 of the specification, the specific inhibition of MMP 13 enzymes is useful in the treatment of a wide variety of degenerative joint diseases, including osteoarthroses.

Baader et al (cited as EP0418797, equivalent to U.S. 5130317) (Baader '317) discloses a class of PDDA compounds which are identified (see col 1, line 9) as inhibitors of the enzymes proline hydroxylase and lysine hydroxylase. Although inhibition of these enzymes may be useful for some therapies, one effect of inhibiting these enzymes is the inhibition of collagen biosynthesis. This is discussed in the third paragraph on page 1 of the present specification. The inhibition of collagen biosynthesis would be a negative effect in the treatment of degenerative joint diseases such as osteoarthritis. Therefore, it is an important aspect of the present invention that the MMP 13 inhibitors disclosed herein also are not proline hydroxylase inhibitors.

In the present rejection under 35 U.S.C. §103(a), the Examiner has cited Barvian as a reference teaching compounds useful as MMP 13 inhibitors. Actually, Barvian identifies a sub-class of PDDA compounds within the scope of the Baader '317 patent. Although Barvian indicates that such compounds are MMP 13 inhibitors, there is no indication that such compounds would not also be proline hydroxylase and lysine hydroxylase inhibitors as described by Baader '317. In the Barvian disclosure, although a family of PDDA compounds is defined, the only example compound is in Example 1, on page 20, namely pyrimidine-4,6-dicarboxylic acid, bis-benzylamide. This reference, and the compounds disclosed therein as well as the Baader '317 patent, are discussed in detail at page 2 of the present specification, where it is indicated that these compounds all have the undesirable property of being proline hydroxylase inhibitors, and thus do not have the selective MMP 13 inhibiting properties of the compounds of the present invention.

To support the distinction over the Barvian reference, experiments were conducted comparing the sole Barvian exemplified compound to examples of the compounds of the

Appl. No. 10/751,545
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Docket No. DEAV2003/0002 US NP

present invention for their proline hydroxylase inhibiting effect. The results are presented in Table 3 on page 37 of the present specification. By test procedures described in detail, Barvian's pyrimidine-4,6-dicarboxylic acid was tested for proline hydroxylase inhibition and compared to a selection of 10 different Example compounds from the present application. The Barvian compound showed an IC_{50} value of $1.2 \mu M$, indicating a clear inhibitory effect. None of the Examples of the present invention showed any proline hydroxylase inhibition. Yet, the compounds of the present were shown to have the desirable MMP 13 inhibitory effect, as discussed above.

From these tests it can be seen that the compounds of the present invention selectively inhibit MMP 13, but do not inhibit proline hydroxylase, while the compound of Barvian has been specifically shown to inhibit proline hydroxylase. Indeed, the class of PDDA compounds disclosed by Baader '317 were identified in that patent as proline hydroxylase inhibitors, which therefore would not have the selective MMP 13 inhibitory properties of the present invention.

For these reasons, the genus of compounds disclosed in Barvian have not been shown to have the unique combination of properties of the compounds of the present invention. Although Barvian identified compounds may act as MMP 13 inhibitors, their was no recognition in Barvian of the importance in the treatment of degenerative joint disease of ensuring that such compounds were not proline hydroxylase inhibitors. Indeed, the only compound actually exemplified by Barvian was shown to be a proline hydroxylase inhibitor.

In the present Final Office Action, the Examiner notes that data in Table 3 of the specification is directed to dicarboxylic compounds rather than dicarboxamide compounds. The Examiner is correct that the compound pyrimidine-4,6-dicarboxylic acid tested in Table 3 is not identical with the compound pyrimidine-4,6-dicarboxylic acid, bis-benzylamide disclosed in example 1 of Barvian (WO02/064571). The compound tested in table 3 does not contain the two "benzylamide" residues. Nevertheless, it is the teaching of the prior art Baader (EP0418797), which is equivalent to US 5,130,317, that the compound pyrimidine-4,6-dicarboxylic acid dibenzylamide is effective in inhibition of proline hydroxylase and

Appl. No. 10/751,545
Reply to Office Action of March 26, 2007

Docket No. DEAV2003/0002 US.NP

lysine hydroxylase. The compound of example 2 in Baader is identical with the compound of Barvian in example 1. A comparison of the processes disclosed in example 1 of Barvian and in examples 1 and 2 of Baader show that the same compound is prepared, although the nomenclature used for the compounds differs a little. Baader shows in the pharmacological example 16 (see also table 1) that the compound according to example 2 (identical with the Barvian compound according to example 1) shows an inhibition of 21% of prolylhydroxylase (table 1). Thus the data in Table 3 of the present specification does clearly show that compound actually exemplified by Barvian is a proline hydroxylase inhibitors. Thus, the cited art clearly teaches away from the present invention as discussed in detail at pages 1 and 2 of the present specification.

Therefore, it is submitted that the compounds of the present invention, and the methods for their use would clearly not be obvious over the teachings of Barvian, and the Examiner is respectfully requested to reconsider and withdraw the present rejection under 35 U.S.C. §103(a).

In regard to the rejections under the judicially created doctrine of obviousness-type double patenting, the Examiner is again requested to defer action pending the identification of allowable subject matter.

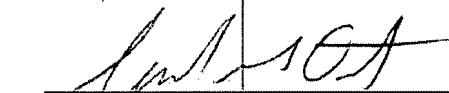
It is submitted that all of the claims in the present application are now in condition for allowance, and action to that effect is respectfully requested.

Appl. No. 10/751,545
Reply to Office Action of March 26, 2007

Docket No. DEAV2003/0002 US NP

The Commissioner is hereby authorized to charge any additional fees or credit any overpayment resulting from this Amendment to Deposit Account 18-1982.

Respectfully submitted,



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